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Editorial

The Editors wish to extend their apologies to the subscribers and advertisers who have been disappointed or inconvenienced by the lateness of appearance of the various issues of the JOURNAL. It is most unfortunate, and has been a source of much concern to the Editors. It is hoped, however, that the subscribers and advertisers will try to understand that there has been considerable difficulty in obtaining copy, and we believe that this difficulty has arisen from the general feeling of unrest which is abroad at this time, and from the fact that fewer and fewer people are being able to find time apart from their daily duties, in which to settle down and write articles.

BLOOD SUBSTITUTES FOR TRANSFUSION

By N. B. TAYLOR, M.D., F.R.S. (C), F.R.C.S. Edin.
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Among the more pressing medical needs of the war is the establishment of means to secure adequate supplies of blood or of a satisfactory substitute for transfusion in haemorrhage and shock. Fresh whole blood is, of course, the perfect transfusion fluid from the purely physiological point of view, but in the stress of an emergency of major proportions the use of whole blood is gravely handicapped by its being available in only limited amounts and by the time required to obtain and bleed a suitable donor. Attempts to build up a reserve store of blood for use in an emergency were made at the beginning of the war. These so-called blood banks have in general been found impracticable, for blood becomes unsafe for transfusion after about 10 days in storage.

When transfusion is undertaken for the treatment of either shock or haemorrhage in a previously healthy person the sole aim is the restoration of the blood volume and consequently of the blood pressure. It is now generally agreed that replacement of the corpuscles is quite unnecessary, for death occurs as a result of a reduction in the *volume* of circulating fluid though the total quantity of hæmoglobin still remaining is far above the level at which the tissues would suffer from lack of oxygen. The fact that whole blood has an enormously greater oxygen capacity than a cell-free fluid such as plasma or serum, or of an artificial solution, gives it no special advantage for transfusion purposes. Indeed, in traumatic shock in which the concentration of red cells is greater than the normal, plasma or serum on theoretical grounds is preferable to whole blood. In haemorrhage whole blood, owing to its higher viscosity, might appear to offer an advantage over plasma or serum, but the difference in viscosity is not great and is a consideration probably of little practical importance. The fluid part of the blood, either plasma or serum, suffers from some of the practical drawbacks of whole blood.

The storage of plasma in the frozen state has been strongly recommended, however, by Strumia and his associates. After it has been thawed the plasma, even though it has been kept frozen for several months, shows no deterioration. Where suitable methods of refrigeration can be established, as in a large general hospital, frozen plasma would appear to be a transfusion material of much promise. For some time it has been used successfully as a routine transfusion material at Bryn Mawr Hospital, Philadelphia. Under special circumstances, e.g., nephrotic oedema or high intracranial pressure, concentrated plasma may be used for its high osmotic effect.

The use of dried human plasma or serum overcomes the two chief disadvantages of blood or of its derivatives in their natural state. In the so-called *desivac* process of Flosdorf, Stokes and Mudd the serum (or plasma) is frozen and dried in the frozen state by exposing it to a high vacuum (0.3 to 0.4 mm.Hg). A plant for processing serum on a large scale by this method has been in operation at the Connaught Laboratories for over a year. All stages in the process, from the collection of the serum from voluntary donors to its bottling, freezing and drying for dispatch overseas, is conducted under the most rigid sterile conditions. The dried product keeps indefinitely. When required for use a sufficient quantity of distilled water is added to the dried material to bring it to the volume of the original serum. After collection the serum from the various donors is pooled without regard to blood grouping. Such pooled serum can be transfused indiscriminately, i.e., into a donor of any blood group.

Dried serum (or plasma) if it is forthcoming in adequate quantities is the best solution of the transfusion problem which has been offered. There is some question, however, whether dried serum can meet the demands for a transfusion material should casualties on a large scale

occur. It is therefore of paramount importance at the present time to search diligently for a suitable blood substitute. Let us then consider some of those materials which have been offered and examine their possibilities for transfusion purposes in the light of experience and of physiological theory.

The requirements of a transfusion substitute are many and may be listed briefly as follows: (a) The molecules (or particles) of the substance must be of such a size that its solution will not leave the circulation too freely. (b) The solution must have an osmotic pressure and

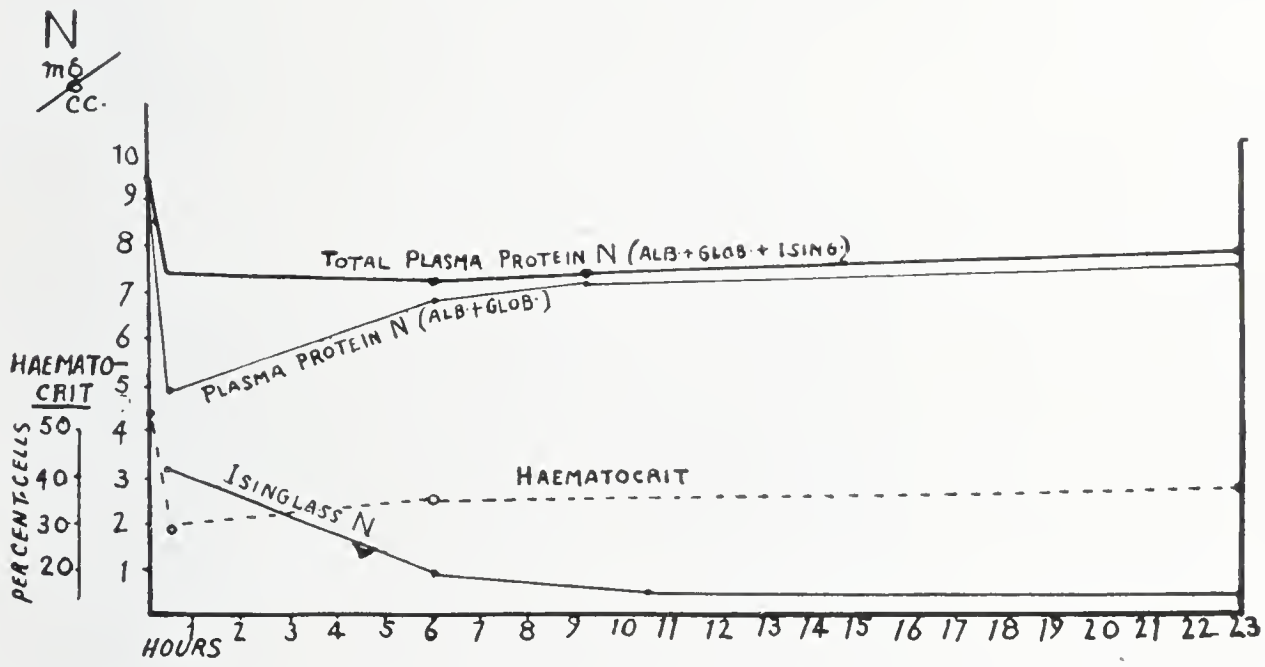

FIG. 1. Showing the concentrations of plasma protein nitrogen (total protein, albumin and globulin and isinglass N) after bleeding and the subsequent transfusion of a 4 per cent solution of isinglass.

transfusion are physical rather than chemical. Blood apparently offers no advantage by virtue of any biochemical characteristic which it possesses.

Though as stated above, under (a), a transfusion material should have a molecule of such a size that it does not escape too freely from the circulation, its retention within the vessels for any great length of time is not necessary or even desirable. It is a rather widely held misconception that the longer a transfusion material is held within the blood stream the more effective it should prove as a blood substitute. It has been assumed, for example, that a material which remained in circulation for 48 hours offered, *ceteris paribus,* better promise than another which disappeared within 24 hours. In the light of recent work our ideas upon this question must be revised. It is now well established that the protein concentration of the plasma, though sharply depressed soon after bleeding as a result of dilution by a protein-poor fluid derived from the tissue spaces, rises rapidly again and approaches the normal value within a remarkably short time. Calvin found, for example, that about 45 per cent of the plasma protein removed by a moderate bleeding (25 per cent of the blood volume) was restored within 30 minutes. Transfusion then should be regarded as a means of tiding the patient

a viscosity approaching as closely as possible these properties of whole blood; these qualifications depend upon molecular size and shape. (c) It should be isotonic with the contents of the corpuscles. (d) It must, of course, be nontoxic and innocuous in every respect. (e) It should not hinder plasma protein production. In addition, the material should be readily available and in large quantities, preferably cheap, capable of being sterilized by simple means and of being quickly prepared for use. Provided a material is suitable for transfusion in the foregoing respects there appears to be no valid objection to the use of some fluid other than blood or its derivatives to fill the vessels after hæmorrhage. The properties which render a fluid suitable for

over a critical period until the loss of circulating fluid has largely been made good. After this has been accomplished transfusion has served its purpose, and if the fluid is of an artificial nature, the sooner that it disappears from the blood stream the better. It may be mentioned here that even homologous blood serum transfused into normal dogs is removed from the circulation in from 24 to 48 hours. It follows from all this that, of the requirements of a transfusion fluid just mentioned, the last one (e) ranks very high in importance.

None of the blood substitutes which have been used in the past answers all the requirements listed above. Some of these will now be described.

Saline solutions. Until the last war saline solution, e.g., physiological saline, Ringer's or Locke's solution, was the only transfusion substitute that was used to any extent; it failed signally. The small molecules of sodium chloride or of any of the other constituents of Ringer's or Locke's solution escape too quickly through the capillary walls and, in consequence, exert little or no osmotic pressure. Saline therefore is capable only temporarily of restoring the blood volume. The viscosity of such solutions is also very low. Their immediate effect on the blood pressure is considerably less than that caused by more viscous solutions and any rise which does occur is evanescent. As a matter of fact, the salt solution in its passage into the tissues carries with it a certain amount of plasma protein, so that the patient may eventually be in a worse state than if saline infusion had not been resorted to. Oedema, especially of the lungs, was not a very unusual result. *Glucose* solution suffers from the same disabilities as does saline.

Gum acacia. Though this material had been used as a blood substitute in animal experiments, not until its introduction by Bayliss in 1916 did it come into clinical use. Gum acacia in a concentration of 6 per cent in physiological saline exerts a colloid osmotic pressure comparable with that of human blood plasma, namely, around 30 mm. Hg. The viscosity of such a solution also closely approaches that of blood. From theoretical considerations then, gum acacia appeared to be an ideal blood substitute and theory seemed to be substantiated by experience. Keith and others in France during the last war found that it rapidly restored to normal and maintained the blood volume and blood pressure. Gum acacia has, however, fallen into disrepute within recent years, for it has been found to interfere with the functions of the liver concerned with the production of plasma protein. After repeated transfusions the liver becomes enormously enlarged; the reticulo-endothelial elements in this organ as well as elsewhere are loaded with the foreign material. The protein concentration of the plasma is seriously depressed and remains so for several weeks after the last transfusion has been given.

Gum acacia is a carbohydrate (a pentosan) which the body cannot metabolize and therefore treats as it does many other foreign colloids. If given in large amounts gum acacia remains in the circulation for a long period, which suggests that in its removal the capacity of the reticulo-endothelial system has been taxed to the utmost.

Pectin solution. Pectin, which is obtained from citrus and many other fruits and is used in the household as a jellying agent, has been employed in a 1 per cent solution as a blood substitute by Hartman and his colleagues. Their results were published last July. The molecule of pectin is composed of a large number of galacturonic acid anhydride units; it has a weight in the neighbourhood of 200,000. The published tracings of Hartman and his associates show that pectin solution raises the blood pressure, depressed as a result of hæmorrhage, to normal and maintains it at a safe level for at least 3 hours. No survival experiments, so far as the writer is aware, have been reported, though a few clinical trials have been made with apparently no ill effects. The effect of pectin upon plasma protein production was not recorded in the paper referred to. Judgment upon the value of this substance as a transfusion material must be reserved until more information is available.

Serum albumin. Cohn and his associates at Harvard for some time past have

been investigating the possibility of using beef serum albumin as a transfusion material, but before the use of this protein is feasible it must be rendered non-antigenic. Researches with this end in view have been undertaken. Human albumin in powder form has also been prepared by Cohn and his associates. When reconstituted by the addition of saline it provides an ideal transfusion material, but like other derivatives of human blood, does not solve the problem of obtaining the necessary supplies of transfusion material.

Isinglass solution. Isinglass or fish gelatin is prepared from the swim bladders (sounds) of certain species of fish, e.g., the sturgeon, hake, cod, etc. The sounds are nearly 85% collagen; when heated to 90°C in water the collagen takes up a molecule of water and is converted to gelatin.

It has been recognized for many years that ordinary gelatin obtained by the hydration of collagenous material in the hides and bones of animals was of a molecular size and (in a concentration of 7 per cent) had a viscosity which should make it an excellent blood substitute. Animal gelatin, however, not infrequently contains the spores of tetanus, and for this reason its use as a blood substitute has been considered too risky. It occurred to the writer that this danger could be avoided by the use of fish gelatin. Isinglass, the common name for the crudely processed sounds, is, strictly speaking, not a gelatin but collagen, for the sounds are at no stage in the manufacture of isinglass subjected to heat. Isinglass is used in large quantities by the brewing and wine making industries. It is therefore available in almost unlimited quantities and is cheap. Its purification for intravenous use is a relatively simple process. The purified product is freely soluble in hot water and can be sterilized immediately before use by boiling for a few minutes.

A 7 per cent solution of the purified material fulfils all the requirements of a transfusion material which have been listed earlier in this paper. It has been proved, in a series of experiments already reported, to be capable of restoring the blood volume and saving the lives of animals which without treatment would almost certainly have died of hæmorrhage. In these survival experiments the blood volume was reduced through bleeding by from 50 to 60 per cent, and the blood pressure to a very low level (14 to 25 mm. Hg). In an independent series of experiments isinglass has been shown to be, like ordinary gelatin, non-antigenic. In some 25 clinical cases in which up to 500 c.c. have been administered in a single transfusion it has been found to be non-toxic and free from any significant reaction.

Isinglass does not disappear completely from the blood stream until more than 24 hours have elapsed. At the end of this time about 10 per cent of the amount injected is still present in the circulation. According to previous ideas, its disappearance might be thought to be too rapid to make it suitable for transfusion purposes. But it is a fact of the utmost importance that the *isinglass does not disappear before natural plasma protein has taken its place.* (See Figure 1.) At the end of 24 hours the concentration of the natural protein of the plasma (albumin and globulin) is not far below the normal value and the blood volume, as evidenced by hæmatocrit determinations, is maintained around the level to which it had been raised by the transfusion.

Isinglass acts, then, as a satisfactory transfusion substitute should, namely, to tide the subject of hæmorrhage over a critical period, and does not interfere with those physiological adjustments which, if given time to become established, will of themselves bring about recovery. The manner in which isinglass serves this purpose is made clearer by a study of the curve of its concentration in the plasma, together with those of the concentration of natural plasma protein (albumin and globulin) and of the *total* plasma protein (albumin and globulin + isinglass). The fall in plasma protein which follows very quickly after the withdrawal of blood is, of course, very largely annulled by the transfusion of the isinglass solution. The curve of total protein (albumin + globulin + isinglass) remains almost level from this time on-

wards, for though the curve of isinglass concentration falls steadily that of the natural plasma protein rises. A reciprocal relationship between the isinglass concentration and the concentration of natural plasma protein is clearly evident.

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HEMOLYTIC TRANSFUSION REACTIONS

By GRANT A. GOULD, '42

Introduction

The phrase "Hemolytic Transfusion Reaction" refers to a severe clinical syndrome which may develop in a patient during or following the intravenous injection of blood and is dependent for its production on hemolysis of the transfused blood cells.

Although many years have elapsed since the establishment of blood transfusion as a relatively safe procedure, serious and often fatal sequelæ are still encountered all too frequently. Careful investigation has disclosed many facts of importance with regard to the etiology of such reactions; much space therefore is allotted to this aspect of the problem in the present article as it is felt that without such knowledge, adequate and intelligent attempts at prophylaxis are impossible. The prevention of transfusion reactions associated with hemolysis becomes doubly important when one realizes the disastrous nature of the train of reactionary symptoms, which scorns all attempts at treatment and usually proceeds relentlessly to effect the patient's demise.

As a prelude to the discussion of these reactions, a historical sketch of the therapeutic use of blood is included and a few of the fundamental concepts of the theory and technique of blood transfusion are reviewed to refresh the reader's memory.

Historical Sketch

Ths use of blood as a therapeutic agent was first inspired by the belief that such a medium was endowed with some mystical and supernatural quality which made it indeed the seat of the soul. Thus it was that Pliny and Celsus described the custom of people rushing into the arenas in ancient Rome to drink the blood of dying gladiators. The middle ages in their turn witnessed the drinking of blood for rejuvenation. The often-cited "transfusion" of the blood of three youths into Pope Innocent VIII was probably of this nature.

It was not however until 1667 that a technique of blood administration was introduced which utilized the intravenous rather than the oral route. In this procedure (the first authentic blood transfusion on record) nine ounces of blood from the carotid artery of a lamb were injected into an arm vein of a young man. The originator of this experiment described the result as "successful" but made reference to the patient passing urine "as black as soot" following the procedure. Modern terminology of course would describe this strange result as "hemoglobinuria", explained by hemolysis of the foreign red blood cells which were introduced into the patient's blood stream. This case therefore constituted our earliest record of a hemolytic transfusion reaction.

To these early scientists, the problems presented by such reactions must have been perplexing indeed; an added burden was the growing indignation of an ignorant and superstitious public which was not appreciably lessened by frequent deaths encountered as a result of this unorthodox practice. Driven finally to animal experimentation, these brave pioneers were able to demonstrate that the transfusion of one animal's blood into an artificially exsanguinated member of the same species was attended with excellent results, but that an animal receiving blood of a different species invariably died. Further than this observation little progress was made and the great riddle "why, unlike animals of the same species, is not the blood of all humans mutually transferable" remained for the time unsolved. The answer was supplied by Landsteiner in 1900. In the most important discovery relating to the transfusion of blood ever made, he showed that all humans were divisible into four great groups according to blood properties. In addition, he demonstrated the necessity of performing certain in vitro tests on blood of both donor and recipient preliminary to transfusion to establish compatibility and thus avert catastrophes due to hemolysis. A phenomenon known as agglutination was noted to invariably pre-

cede hemolysis; thus by the use of agglutination tests, the probability of ensuing hemolysis could be recognized and a fatal reaction forestalled.

The Agglutination Factors

Landsteiner's original concept of the individual differences in human blood was based on the postulation that there existed two separate and distinct antigens, the property of erythrocytes only, and two corresponding antibodies, resident in blood plasma. The antigens were termed agglutinogens, designated by the symbols "α" and "β" respectively; the antibodies became known as agglutinins and were tagged "α" and "β". Under natural conditions, an agglutinogen and its corresponding agglutinin cannot be present simultaneously in the same blood. If, however, blood of an incompatible group is introduced by means of transfusion, the antigens of the injected red cells are met by their specific antagonists (the corresponding agglutinins) contained in the recipient's serum and agglutination takes place.

On this basis of agglutination therefore, the blood of all humans was divided into four great groups according to the agglutinogens each contained (O, A, B, AB). This classification, the only one receiving international acclaim, remains the simplest and most scientific means of group identification; two others are in popular use but are a source of confusion and should be discarded. The incidence of the various groups among the North American population is approximately as follows:

Group O	45%
Group A	42%
Group B	10%
Group AB	3%

Coincident with Landsteiner's great discovery was the introduction of a simple test to determine an individual's blood group as well as a cross-matching technique to confirm the result and ensure compatibility of both donor's and recipient's blood. The routine application of such methods served to salvage the use of blood transfusion from the status of a medieval novelty, at best a hazardous procedure, and place it as an invaluable life-saving weapon in the hands of the medical profession.

Grouping and Cross-matching Technique

For these tests, samples of blood from both donor and recipient must be obtained and each then separated to yield a weak suspension of red blood cells as well as a sample of clear serum. The former is obtained by the addition of one drop of blood to 10 cc. of 2% sodium citrate in saline; the latter by centrifuging 10 cc. of blood and pipetting off the supernatant serum as required. Our materials therefore now include recipient's cells (RC), recipient's serum (RS), donor's cells (DC) and donor's serum (DS). In addition, samples of standard group A and B sera are required for the grouping technique. All tests are best performed on a suitably labelled thick glass plate, containing several shallow depressions to contain the preparations now outlined. In every case, the standard proportion of one drop of cell suspension to two drops of serum is used and the frequent agitation of the plate by a mild rotary motion, enables suitable mixing of the cells and sera to occur. Grouping consists merely of observing the results following the mixing of samples of the unknown cell suspensions with standard A and B sera. Reference to the accompanying diagram will readily show that agglutination obtained with both A and B denotes group AB; with neither, group O; with A alone, group B, and with B alone, group A.

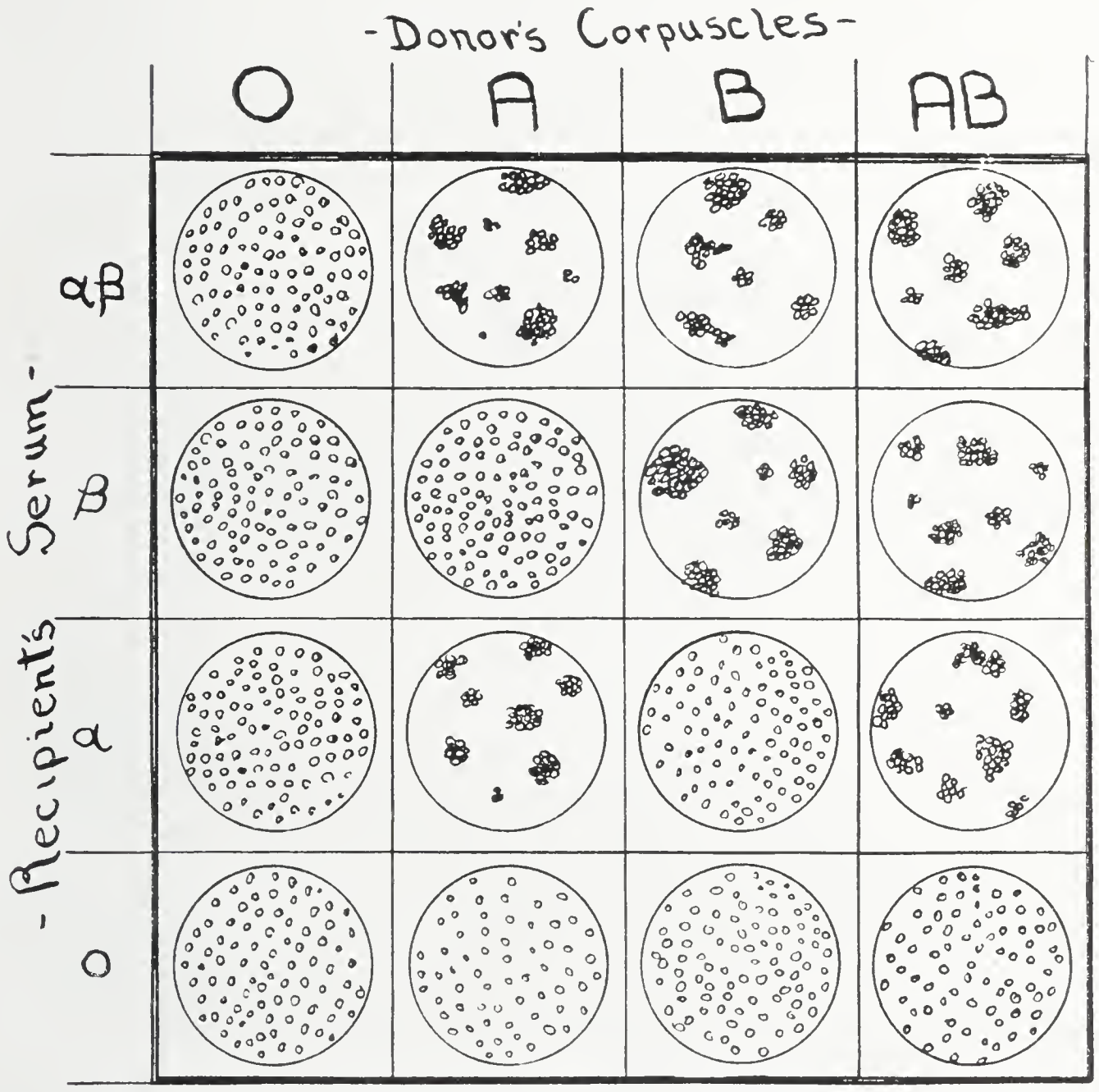
Since during a transfusion, the agglutinins of the donor's serum are rapidly diluted and probably absorbed, they are of little consequence in the production of untoward reactions. This set-up therefore in vitro is termed the "minor cross" and is represented by allowing the interaction of DS and RC. Minor agglutination is to be expected when group O blood is administered to a recipient belonging to any other group and similarly when a group AB recipient receives any other than group AB blood. The all-important determination however is whether the recipient's serum will agglutinate the

donor's cells; the experimental representation of the co-existence of these two factors is termed the "major cross". Agglutination therefore in the presence of DC and RS foretells a dangerous hemolytic result and contraindicates the transfusion of such blood.

Results in the above are interpreted both macroscopically and miscroscopically, allowing a minimum of twenty minutes for the thorough admixture of the component factors.

RELATIONSHIP OF AGGLUTINATION FACTORS

(*microscopic appearance*)



Other Agglutinogens

No mention has so far been made of the M, N and P agglutinogens, known to be present in human blood. These factors are only identifiable by special methods and as they fail generally to stimulate antibody formation on being injected, their importance is largely confined to experimental genetics and forensic medicine. (U. of T. M.J. 15-79-37). The sub-groups of agglutinogen A and a newly discovered "Rh" agglutinogen however demand further consideration and will be discussed under the heading of "Etiology".

Source and Administration of Blood

For several years, cadavar blood from cases of sudden death has been used successfully in Russia, but the æsthetic implications of such a method have so far restricted its popularity elsewhere. Reinjection of lost blood (autotransfusion) is not to be recommended except in cases of dire emergency and even then is contraindicated in the presence of infection,

malignancy or ruptured hollow viscus. Placental blood has fallen into disrepute as a practical source of blood for transfusion purposes and it too can be readily dismissed.

The reactions considered below are those encountered during the use of citrated human blood, collected in the routine manner and transfused intravenously by the drip technique. The rate of injection varies considerably as recommended by different authorities but ranges generally from 5 to 100 cc. per minute.

Clinical Picture of Hemolytic Reaction

Although the pattern of signs and symptoms in all cases of hemolytic reactions as described in the literature is extraordinarily constant, considerable variation occurs in the degree of severity and time of onset of these.

An immediate reaction may follow the introduction of a comparatively small quantity of blood and is first evidenced by the onset of restlessness, pallor, dyspnea, feeble rapid pulse and fall in blood pressure. Following closely on this initial picture of shock may be any or all of: cough, vomiting, cyanosis, pain in the lumbar region and, finally, cold clammy skin.

A more delayed type of reaction is heralded by the onset of chills and fever, occurring usually from thirty to sixty minutes after the commencement of the transfusion. Hemoglobinemia and hemoglobinuria are characteristically present, accompanied by a transitory jaundice.

Approximately 40% of patients demonstrating either of the above syndromes have complete recovery. The majority however have a short remission following the acute onset of symptoms after which they develop signs of renal insufficiency with oliguria or anuria, nitrogen retention, and uremia. Death usually supervenes in from four to ten days, in the wake of edema, convulsions and coma. A few however, have a marked diuresis which presages the complete subsidence of symptoms and recovery. The longest oliguria on record with recovery is 16 days. Treatment is of little avail and the mortality rate in hemolytic reactions is generally agreed to be about 62%.

Etiology

Although reactions following the transfusion of blood are not infrequent, the great majority of these are of a non-hemolytic nature, characterized by fever or rigors which are transient and not a threat to life. As exceptions to the above it must be remembered that, as in any serum therapy, reactions based on sensitivity phenomena may occur and also that the over-rapid administration of blood to a patient with a weakened myocardium may produce disastrous results (speed shock) by reason of the sudden extra load imposed on the right side of the heart. In addition, syphilis, malaria or and bacteremia present in a donor may be transmitted to the recipient; special care must therefore be exercised to exclude such possibilities when selecting a donor.

We are here concerned only with those reactions dependent on the presence of hemolysis and from the standpoint of etiology, these may at once be classified into three great groups as due to—

(1) Extra-group incompatibility.
(2) Intra-group incompatibility.
(3) Improper handling of blood.

(1) Extra-group Incompatibility

The term "extra-group" is used to donate incompatibility in the presence of blood of the heterogeneous group, an example being the transfusion of group A blood into a group B patient. It is readily evident that faulty laboratory technique with resultant mistakes in blood grouping must account for most of these. The commonest errors leading to tragic results are the following:

(1) Careless mixing of labels.
(2) Low titred or contaminated testing serum.
(3) Weak agglutination factors in the tested blood.
(4) Pseudo-agglutination.
(5) Auto-agglutination or cold-agglutination.
(6) Sub-groups.

The most inexcusable of all the above errors is the careless mixing of labels. By this simple act, a nurse, orderly, or laboratory technician may unwittingly seal the doom of a patient.

Unreliable results may be expected with the use of low titred or contaminated testing serum; sufficient potency should be present to cause the agglutination of the specific iso-agglutinogen in a dilution of 1 in 10, using a 2% cell suspension. Such serum must be kept at ice-box temperature and discarded when it becomes cloudy.

Pseudo-agglutination or pronounced rouleaux formation is easily recognized by the experienced observer but is rarely encountered if the recommended proportions of cell suspension (2%) and sera are used. The addition to the preparation of one drop of a specially prepared lecithin suspension serves to remove pseudo-agglutination but causes no diminution in true agglutination and is therefore of great value in doubtful cases. The active principle of the serum is not absorbed in pseudo-agglutination which is in marked contrast to what occurs in the true type.

A non-specific reaction occasionally occurs in blood which has been standing for a few days. This phenomenon is known as "auto" or "cold" agglutination and may occur normally at ice-box temperature. When it takes place at room temperature however one should be careful to rule out such pathological conditions as syphilis, paroxysmal hemoglobinuria and severe anemia. It may moreover lead to difficulty in grouping and be confused with group AB; in cases where doubt exists, simple washing of the red blood cells in saline prior to the test will eliminate any non-specific auto-agglutination factor. In contrast to pseudo-agglutination, cold agglutination resists slight or moderate dilutions and the agglutinins are absorbable by the cells. Cold agglutination moreover is never present at body temperature but may exist at room temperature.

The sub-groups A1 and A2 sometimes lead to confusion in grouping since the A2 agglutinogen is extraordinarily weak and therefore delays agglutination to a considerable degree. A minimum test of twenty minutes is thus recommended before an opinion can accurately be given on the result of a grouping or cross matching. The reason that errors from this source are not more frequently followed by serious or fatal reactions is that agglutinable factors too weak to be detected by routine grouping are also too weak to cause a marked reaction.

Intra-group Incompatibility

Under this heading reference is made to unexpected reactions occasionally encountered when blood, proven to be of the homologous group, is transfused. The clinical picture in such cases is identical with the classical reaction described in a previous section; the etiology however is still a matter for much conjecture. Admittedly such reactions are rare, less than twenty authentic cases having appeared in the literature to date.

Evidence has recently been presented to suggest the underlying cause of these mysterious reactions to be an agglutinogen, designated 'Rh". This factor has the property of stimulating the production of an Rh. antibody in certain persons lacking the agglutinogen. If sufficient time elapses following a transfusion for the development of this anti-Rh agglutinin, and a subsequent transfusion of Rh positive blood is given, a hemolytic reaction may be expected. In accordance with this explanation, it may be noted that all proven intra-group reactions belong conspicuously to one of two classes:

(1) Patients who have had more than one transfusion.

(2) Intra or post-partum females.

The latter class is explained by the fetal inheritance of the Rh agglutinogen from the father and its subsequent reabsorption with the production of Rh antibodies. One transfusion therefore to such a patient suffices to preduce a hemolytic reaction. The technique for the identification of this agglutinogen is described in U. of T. M.J., 19-102-41, and consists essentially of a major cross agglutination test performed at low temperature. A postive result rarely is evidenced by more than a granularity and as yet no suitable explanation is forthcom-

ing to account for the discrepancy between such a mild in vitro reaction and the severe in vivo results. Recent work by various experimenters has confirmed the existence of this Rh factor as a true agglutinogen, having antigenic properties and estimated to be present in 85% of the population.

Improper Handling

Severe agitation of blood during or following its collection from the donor and frequent temperature changes are to be avoided. These factors are known to produce certain incipient coagulative changes which may result in agglutination and hemolysis on reaching the circulation. Such changes however are too fine to be detected by ordinary methods and it is therefore all-important that they be avoided by meticulous care in the handling of blood prior to transfusion. Fatal cases of hemolysis are on record which followed the indiscreet heating of blood before transfusion. It is interesting to note in this regard that no untoward symptoms follow the transfusion of blood at a moderate rate immediately after its removal from storage at 4 degrees centigrade. Some authorities have therefore advocated that blood should be used without preheating it.

One must maintain a constant vigil against bacterial contamination from the moment the donor's blood is taken until the transfusion has been completed. The sterile collecting flask should, on receipt of the donor's blood, be stoppered immediately with sterile gauze and cellophane and if not to be used at once should be stored at a temperature of 4 degrees centigrade. The report of a fatal hemolytic reaction due to bacterial contamination is to be found in the autopsy records of the Toronto General Hospital. The causative organism in this case proved to be an aerobic spore-bearer and death ensued within six hours of the transfusion as the result of bacterial hemolysis.

Pathology

The characteristic lesion of a hemolytic reaction is to be found in the kidney; such an organ is often termed "transfusion kidney". Tubular necrosis is a marked feature of the microscopic pathology and masses of altered blood pigment, leucocytes and desquamated epithelial cells may be found impinged in the lumina of some of the tubules. Occasionally there is an accompanying central necrosis of the liver.

The most popular pathogenic theory of the anuria and uremia in fatal cases is based on mechanical blockage of the tubules by the breakdown products of hemoglobin. The fact however that hematin granules are seldom found in more than 15% of the tubules largely discounts this attractive theory since this is probably less than the number of nephrons functioning at any one time and therefore clearly insufficient to produce renal suppression. The answer to the puzzling problem in pathogenesis may ultimately be found in a histamine-like toxin, liberated by hemolysis and producing tubular necrosis. The osmotic inbalance thus produced would have the effect of preventing urinary excretion and forcing the reabsorption of toxic metabolites with resultant uremia.

Conclusions

In the reduction of post-transfusion fatalities, our attack must be directed toward prevention rather than treatment. In this connection the following points should be observed:

(1) Employ only full-time experienced technicians to ensure competent performance and interpretation of preliminary compatibility tests.
(2) Use cross matching and cold tube tests routinely in addition to the usual grouping procedures, to establish compatibility.
(3) Select only healthy, fasting, Wassermann-negative donors with no history of malaria or hypersensitivity reactions.
(4) Avoid undue agitation or indiscreet heating of blood prior to transfusion.
(5) Be reluctant to transfuse blood which has been standing more than 10 days and refuse to use blood showing evidence of hemolysis.
(6) Demand close observation of the patient at all times during the transfusion and order the procedure to be stopped immediately at the first sign of an untoward reaction.

VITAMIN C (ASCORBIC ACID)

By T. G. H. DRAKE, M.B.

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This substance, originally known as the antiscorbutic vitamin through its effect in preventing scurvy, came to be known as vitamin C about 1920. In 1927 and 1928, Szent-Györgyi in a study of reducing substances in various tissues isolated in crystalline form a compound, $C_6H_8O_6$, hexuronic acid. While Szent-Györgyi regarded this substance as being associated with vitamin C, he did not believe it to be that substance itself. In 1932, King and Waugh announced the isolation of vitamin C in crystalline form and stated that the substance was apparently identical with the hexuronic acid of Szent-Györgyi. Within a month Svirbely and Szent-Györgyi announced that they had been able to prevent the development of scurvy in guinea-pigs through administration of hexuronic acid, which substance they stated was identical with vitamin C. In 1933, the substance was named ascorbic acid. Due to the therapeutic suggestiveness of the name ascorbic acid, the Council on Pharmacy and Chemistry of the American Medical Association advocated the name cevitamic acid, but due to the widespread use of the term ascorbic acid among scientists, they finally assented to the use of that designation for vitamin C. Since 1933, ascorbic acid has been synthesized, methods for large scale production have been developed, and the pure substance is widely available.

Ascorbic acid is $C_6H_8O_6$ containing a 1-4 lactone and a 2-ene-diol linkage. It is a white crystalline material, freely soluble in water. Free ascorbic acid may be reversibly oxidized to dehydroascorbic acid, and this further oxidized to an irreversibly oxidized form, this latter having no antiscorbutic effect. Copper acts as a catalyst for the oxidation of ascorbic acid. Ascorbic acid is unstable in alkaline solutions and is destroyed by visible light. In many vegetables and fruits, but not in citrus fruits nor tomatoes, oxidases are present which bring about extremely rapid destruction of this vitamin when—in the raw fruit or vegetable—cells are broken up by juicing or fine grinding. Since ascorbic acid is water soluble, losses up to 50 per cent or more may occur in discarded cooking water. Prolonged cooking, especially after alkalinization by sodium bicarbonate, will also bring about loss of the vitamin.

The estimation of ascorbic acid.

After the experimental production of scurvy in the guinea pig in 1907, many facts regarding the distribution of vitamin C in foods were learned. On a vitamin C free diet guinea pigs cease to grow, lose weight and develop tenderness with hæmorrhages about the joints. In the incisor teeth abnormalities in the laying down of enamel and dentin occur. In the biological estimation of ascorbic acid the amount of the substance is determined which must be fed daily to prevent these scorbutic changes. In 1932, Tillman and his associates discovered the correlation between the antiscorbutic value of substances and the amount of 2,6 dichlorophenolindophenol which they would reduce. While this reduction of indophenol is not absolutely specific for ascorbic acid, through this quantitative reaction one has been able to make estimations of vitamin C rapidly, with a good deal of accuracy, and also on quantities too small for biological tests.

The state of ascorbic acid nutrition of the individual may be assessed by estimation of its level in the blood, and through saturation tests. In blood plasma, fasting levels of from 1.4 to 0.6 mg. per 100 c.c. are considered normal; values as low as 0.0 may be obtained. The degree of saturation of the body as regards vitamin C may be estimated by measurement of the amount of ascorbic

acid excreted through the urine after the ingestion of 300 mgs. of pure ascorbic acid. Adults on an ordinary diet, including 1 orange or half a grapefruit daily, usually excrete from 25 to 100 mgs. ascorbic acid through the urine in the four hours following the administration of the 300 mgs. of ascorbic acid. Excretions of less than 5 mgs. per 100 c.c. of urine are indication of a lowered state of vitamin C nutrition.

Ascorbic acid requirements.

The recommended daily requirements for ascorbic acid as laid down by the Committee on Food and Nutrition of the National Research Council, Washington, are the following: Infants, 30 mgs.; children 1 to 12 years, 35 to 75 mgs.; children over 12 years and adults, 70 to 100 mgs.; in pregnancy and lactation, 100 to 150 mgs.

In the past, since scurvy does not occur before 4 months of age, it was thought sufficient to commence the administration of vitamin C at 3 months of age. However, on account of the abnormally low blood ascorbic acid values found before that time, practically always in the artificially fed infant, and occasionally in the breast fed infant, an antiscorbutic should be started—at least in the bottle fed infant—in the lying-in hospital, or at latest by 1 month of age. Unless one can be absolutely sure of the adequacy of the ascorbic acid intake of the lactating mother, vitamin C should also be administered to the breast fed infant. Certainly it will do no harm and the chance of refusal is less the younger the administration is started. The 30 mgs. prophylactic dose of ascorbic acid recommended during infancy is contained in approximately 2 ounces of orange juice or 6 ounces of tomato juice. The orange juice should be administered unsweetened, diluted with an equal amount of water, in the interval between feedings. The tomato juice may be given undiluted. Pure ascorbic acid may be administered if desired or, if the orange or tomato juice produce gastro-intestinal disturbance. The tablet of ascorbic acid should be dissolved in a little water and mixed with the feeding just before its administration.

Ascorbic Acid Content of Fruit and Vegetables

Ascorbic acid is present in all fresh leafy greens and root vegetables, fruits and berries in amounts per 100 grams ranging from over 1000 mgms. in rose hips (the red seed pods of roses) to 10 mgms. in carrots. Excellent sources of ascorbic acid are black currants, red and green sweet peppers, cabbage, brussels sprouts, turnips, cantaloupes, oranges, lemons, grapefruit, and tomatoes. While vitamin C is relatively stabile in the citrus fruits and tomatoes, it is quite perishable in vegetables, especially in the green leafy varieties. Warehouse storage, even at 32° F., causes marked loss in spinach. Spinach harvested in the fall, which when placed in commercial cold storage contained 40 mgms. or more ascorbic acid per 100 grams, on removal for sale two or three months later, though perfectly satisfactory in appearance and taste, may contain only 1 or 2 mgms. ascorbic acid per 100 grams. Iceberg lettuce shipped from California and Arizona in refrigerator cars and actually packed in ice, frequently contains only 1 or 2 mgms. of ascorbic acid when retailed in Toronto. In the period of holding in the retail store, locally grown leafy greens frequently lose one-half their vitamin C content without developing any appearance of wilting. In cooking vegetables under ideal conditions—that is for the shortest period of time with the minimum amount of water—50 per cent of the ascorbic acid may be destroyed. By cooking for too long a period, and especially in too much water, practically all the vitamin C may be lost. Under modern commercial canning procedures, where most of the heat treatment is carried on after closure of the can, the loss of ascorbic acid is much less than in home canning. Certainly commercially canned vegetables contain more ascorbic acid than home cooked 'out of season' vegetables which have been transported long distances. In Toronto,

weekly examinations of fresh orange and grapefruit juice over the past six months have shown an average ascorbic acid content per 100 c.c. of 51 mgms. in orange juice and 43 mgms. in grapefruit juice. In the summer of 1941, the average ascorbic acid content per 100 c.c. of several brands of canned orange juice was found to be 48 mgms. and of canned grapefruit juice, 36 mgms. The average value of new 1941 crop of canned tomatoes and canned tomato juice was 18 mgms. per 100 c.c. Canned pineapple juice contained about 15 mgms. per 100 c.c. Sweet apple juice, fresh or canned, and juice from stewed prunes contain practically no vitamin C. The loss of ascorbic acid in freshly expressed orange or grapefruit juice, or canned orange, grapefruit or tomato juice after opening the tin, brought about by 24 hours storage in the refrigerator, is negligible.

Scurvy.

Scurvy is a deficiency disease due to a lack of vitamin C. The usual complaint is that of pain and tenderness on handling. An artificially fed infant, over 4 months of age, which had previously been doing well ceases to gain or loses weight and becomes pale, fretful and irritable. The infant begins to cry when moved and is disinclined to bear its weight on its feet; swelling and redness occur about the erupted or erupting teeth, and tender swellings may appear about the ends of the long bones.

Scurvy occurs practically only in the artificially fed infant. The disease is extremely rare before 4 months of age, occurs most frequently around 10 months of age, and is very uncommon after 15 months. In the past, many cases of infantile scurvy have been mistakenly diagnosed rheumatism, a disease which does not occur before 3 years of age. Scurvy is uncommon in infants who from an early age are fed "bits from the table" since these in their very mixed diet, frequently productive of digestive upsets, receive a small amount of vitamin C.

Where vitamin C is lacking, the endothelial and mesothelial cells lose their power to produce intercellular collagen or collagen-like substances, the foundation of all fibrous tissues. As the result of defects in the cement substance lying between the single layered walls of capillaries, hæmorrhages occur. Defective osteoblastic function leads to non-ossification of growing bones. In the teeth abnormalities in the laying down of enamel and dentin result. In addition to abnormal formation, resorption of these substances also occurs. Physiologically ascorbic acid plays a role in cellular oxidation-reduction reactions.

In scurvy the face presents a worried expression, the child is irritable, and if the condition is very acute may cry whenever anyone approaches the bed for fear it may be moved. The patient lies flat on its back, the legs flexed at hip and knee joints, the thighs externally rotated, the legs resting on the bed. The infant is disinclined to move and does not attempt to bear weight on its feet. The skin may show large black and blue areas resulting from slight unobserved trauma, as on the forehead or shins, or a few small ecchymotic spots. Obscuring more than the ordinary amount of the erupted teeth, the gums are purplish-red, swollen and spongy, and bleed easily. Over the erupting teeth the gums are engorged. The costo-chondral junctions of the ribs exhibit a sharp angular deformity, in contradistinction to the smooth rounded deformity of the rickets rosary. Frequently the sternum and cartilages may be displaced backwards, producing a sharp step-like deformity. At the end of the long bones, especially at the lower ends of the femurs, tender swellings may be found. These tumors are due to hæmorrhage beneath the periosteum and do not involve the joint cavity. In acute scurvy the patient's temperature is usually elevated to from 100° to 102°, this falling to normal in a few days under treatment. The pulse rate is usually elevated. A secondary anæmia, which must be accounted for by poor hæmoglobin formation rather than loss of blood by hæmorrhage, is present.

The effect of adequate treatment is

dramatic, and the result of treatment may be used as a point in diagnosis. Within 24 to 48 hours the infant is much more comfortable, the irritability has decreased greatly and tenderness has lessened. Within 48 to 72 hours the gums are less purplish, less swollen and less apt to bleed.

In acute scurvy the plasma ascorbic acid content is zero. However, while the presence of a normal content of ascorbic acid, 0.6 mgm. or more per 100 c.c. plasma, is sufficient to rule out scurvy, many individuals, both infants and adults, having no ascorbic acid in the blood will show neither clinical nor x-ray evidence of scurvy.

X-Ray Changes in Scurvy

As pointed out by Edwards A. Park, the typical x-ray picture in scurvy is the result of two processes, improper laying down of new bone, consisting of calcification without ossification, and increased resorption. At the growing ends of the long bone there is progressive formation of cartilage cells and calcification of intercellular substance, but the osteoblasts do not function normally and no ossification occurs. In scurcy this calcified lattice, which normally varies from one-tenth to three-tenths of a millimeter in thickness, gradually increases to about one millimeter in thickness. In the x-ray plate this chalky, easily fractured lattice—on account of its increase in density and width—shows up as a wide dense white line at the ends of the long bones, especially at the ends of the femurs, and produces a halo-like appearance surrounding the epiphyses. At the same time there is increased resorption of the bone which had previously been laid down. This destruction of preformed bone, while bringing about loss of trabeculation and giving the x-ray of the shaft a ground-glass appearance, is greatest where normally bone growth is most active and forms a zone of rarefaction which gradually extends from the cortex across the bone on the shaft side of the lattice. Through increased permeability to the x-ray this zone of rarefaction shows up as a dark area on the x-ray plate. In the earliest stages this rarefaction zone shows up as small clefts or crevices just underneath and on the shaft side of the lattice, and extending in from and including the cortex. Fractures of the cortex and lattice occur, frequently extending entirely across the bone with separation of the epiphysis and greater portion of the lattice from the shaft. It is most important to remember that the tumors at the end of the long bones due to haemorrhage beneath the periosteum do not show up in the x-ray in the acute stage. However, after daily administration of a therapeutic dose of ascorbic acid for 8 to 10 days, new bone is laid down beneath the stripped-up periosteum and the tumor is plainly visible.

To recapitulate, the x-ray signs of scurvy in the x-ray plate are a dense white line at the ends of the long bones, a halo-like appearance about the periphery of the epiphyses, a darkened area, the zone of rarefaction, on the shaft side of the lattice, fractures of the lattice which may bring about separation of the epiphysis and the greater part of the lattice from the shaft, a general ground-glass appearance of the shaft and, only after healing has begun, the outlining of the subperiosteal haemorrhage.

Treatment of Scurvy

The daily administration of 6 to 8 ounces of orange or grapefruit juice, 16 to 20 ounces of tomato juice, or 100 to 200 mgms. of pure ascorbic acid will be adequate to produce rapid cure in practically all cases. If necessary through poor gastro-intestinal absorption, ascorbic acid may be administered intramuscularly or intravenously.

VITAMIN K

By C. S. SNELLING, M.B.

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The anti-haemorrhagic vitamin K is one of the recently used vitamins and in the space of a few years a great deal has been learned regarding the source, synthesis, action and clinical application.

Dam of Copenhagen and various other investigators from 1929 on have noted a bleeding tendency in chicks which were fed certain types of artificial diet used in the investigation of sterol metabolism. By 1935 Dam and Schonheyder recognized that the deficiency factor was a fat soluble substance different in nature from vitamin A, D or E and it was present in hog liver, hemp seed, cereals and vegetables. It was named by these investigators as vitamin K from the word Koagulatins vitamin. The non-saponifiable portion of hog liver fat, alfalfa and other substances containing the factor was shown to be the effective portion. Schoenheyder showed that the bleeding tendency in the chick was a result of low blood prothrombin and this was raised when foods containing this vitamin K were fed to the chick.

Holst and Halbrook in California described a similar disease in the chick which was cured and prevented by feeding fresh cabbage. Further work by these, revealed that an ether extract of alfalfa and putrified fish meal prevented the condition.

Almquist and Stokstad were able to confirm Dam's work, and Almquist produced a purified crystalline fraction from alfalfa with vitamin K properties. They showed that bacterial action in the bowel produced this vitamin and that the contents of the lower bowel contain a large quantity of this anti-haemorrhagic substance.

Haemorrhagic disease due to vitamin K lack in the diet can be produced in chickens, ducklings and goslings, but not in rats, guinea pigs or dogs. The reason for this is probably because absorption from the lower part of the intestine is very poor in fowl.

Quick in 1937 suggested on the theoretical basis that because bile salts were necessary for fat absorption, vitamin K might be of value in combatting the bleeding tendency associated with obstructive jaundice and biliary fistula. Shortly after this it was established by various investigators that the prothrombin of the blood was low in obstructive jaundice and biliary fistulae both experimentally and in the human. Soon successful alleviation of the low prothrombin in experimental animals and in patients with obstructive jaundice was attained by administering vitamin K and bile salts together. This established the fact that bile salts were necessary for the transfer of the fat soluble vitamin K from the bowel to the blood stream.

Quick developed a method which was of use clinically for the estimation of the prothrombin of the blood and as a result of this and further developments of new methods, it has been established that the prothrombin of the blood is lowered in obstructive jaundice, biliary fistula and in the newborn period. The factors necessary for the production of prothrombin have been shown as follows—a source of vitamin K, bile salts for its absorption, digestion of fats, proper intestinal absorption and a functioning liver.

Almquist and Klose, McKee, Binkely, Macorquodale, Thayer and Doisey, Dam and Ansbacker and Fernholz established that crystalline vitamin K obtained from natural sources was a quinone. That obtained from alfalfa was called vitamin K1, and that from putrified fish meal vitamin K2. They had the same quinone structure with a different side chain. Soon it was shown that synthetic quinone compounds had vitamin K activity, and of these, 2 methyl 1-4 naphthoquinone was found to be one of the most potent sources, much more than natural vitamin K. This is soluble in oil but very slightly in water. Subsequently esters and salts of this have been made which are water

soluble. These latter may be unstable. Weight for weight they are not as active as 2 methyl 1-4 naphthoquinone, but molecularly they are as active because the molecule of these compounds is much larger.

The various methods that have been evolved for the estimation of prothrombin have as their basis Howell's theory of blood clotting, which is as follows: the prothrombin of the blood when acted on by thrombokinase or thromboplastin in the presence of calcium changes to thrombin. This thrombin unites with or activates the fibrinogen to form fibrin or clot. The methods that are employed to estimate prothrombin are carried out on plasma or whole blood that has been prevented from clotting by the use of oxalate which neutralizes the calcium, or heparin which removes the natural thrombokinase or thromboplastin of the blood. Oxalated blood is recalcified and heparinized blood has an excess of thromboplastin added, then the time for clot formation is measured. On the assumption that all the other factors are equal it is taken for granted that differences in time are due to varying amounts of prothrombin. As a result of this, many investigators estimate prothrombin in percent or units, assuming a certain time is normal and longer time is a percent of normal. In any event, a short clotting time of the recalcified plasma indicates a good prothrombin content and a prolonged time indicates a poor prothrombin content of the blood. For most of the estimations reported the method described by Quick has been used, which consists of mixing oxalated plasma with a thromboplastin solution, recalcifying and observing the time necessary for clot formation to take place in the mixture. The thromboplastin solution is obtained by making a saline extract of dried rabbit's brain which had been dehydrated with several changes of acetone. The dried brain should not be kept for more than one week. A bedside method has been developed by Smith, Warner and Brinkhous for use with whole blood, which consists in adding blood directly to thromboplastin solution and calcium solution and measuring the time for clot formation. With this method a normal control must be done at the same time. These same investigators have developed a quantitative method for the estimation of prothrombin but the technique is so complicated that it is employed by only a few laboratories engaged in research on blood clotting function.

Micro methods have been devised and one of these consists in mixing one part of oxalate solution with nine parts of blood obtained from a capillary puncture of the patient, in a micro pipette. Thromboplastin and calcium chloride solutions are added and the time for clot formation noted. This is a very useful method in small patients when venous puncture is difficult.

Using the various methods for prothrombin estimation it has been shown that lowered prothrombin of the blood is present in haemorrhagic disease of the newborn and that when haemorrhagic disease is cured the prothrombin of the blood is normal. Various types of vitamin K have been used in the treatment of haemorrhagic disease. At first synthetic vitamin K in oil was administered by mouth, and if this was retained it was effective in causing a rise in the prothrombin with cure of haemorrhagic disease. Later other forms of synthetic vitamin K compounds have been made which are suitable for intravenous and intramuscular use. These are effective in curing haemorrhagic disease of the newborn. The types used go under various trade names. 2 methyl 1-4 naphthoquinone dissolved in corn oil is used intramuscularly, and 2 mgms. is effective in from 2-4 hours in controlling the haemorrhage. Other water soluble preparations are of value which may be used intravenously.

Newborn infants have a lowered prothrombin which normally disappears by 6 or 7 days of age. This low level in the newborn may be so marked that the patient will bleed if an injury is sustained. This factor must be appreciated in the birth and handling of a newborn infant. It has been shown that if mothers are given synthetic vitamin K before the delivery of the baby, extremely low levels of prothrombin in the baby are avoided. This vitamin K may be administered by

mouth or parenterally. The dose by mouth is 5 mgms. in corn oil which is effective when given near the delivery of the baby but more than 4 hours previously. This is more effective than giving a smaller dose daily for some time prior to the delivery of the baby. The usual practice is for the mother to take the vitamin K at the onset of labor. It may be given intramuscularly or intravenously if more speedy action is required or it is not retained by mouth. It is the custom in most hospitals now to order a dose given to the mother at the onset of labor. If the delivery is less than 4 hours after or the vitamin K is vomited or the delivery is difficult and prolonged or the baby is premature, the baby should receive a parenteral injection at birth as well.

Vitamin K given to the mother has no effect on her prothrombin but it does protect the baby from the likelihood of haemorrhage due to low prothrombin.

The other place for vitamin K therapy is connected with liver disease. The prothombin of the blood is lowered if bile does not enter the intestine, thus aiding in the absorption of fat soluble vitamin K. In biliary obstruction or fistulae the prothrombin of the blood is lowered. This effect is not immediate but takes weeks to occur so that immediately after biliary obstruction one does not need to fear this change. However, in operations on long-standing biliary obstruction or fistulae, it is necessary to give vitamin K. This can be given by mouth in conjunction with bile salts, or parenterally. It will then act on the liver to raise the prothrombin.

In liver disease such as toxic hepatitis and cirrhosis the prothrombin of the blood may be low. In these instances vitamin K will have no effect in raising the prothrombin because it only acts with a relatively normally functioning liver.

The minimum effective dose has not been determined. No untoward effects have been observed from large doses in humans. The actual human requirements from dietary sources have never been determined. The best food sources are whole grain cereals, liver and green leafy vegetables.

BURNS AND SOME MODERN METHODS IN TREATMENT

By IAN P. TODD, '44

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Before the start of this war, the treatment of burns was considered to be satisfactory. It was very soon found that this was not the case. It seems therefore that ideas gained at St. Bartholomew's Hospital, London, during the blitz of 1940-1941, and from the Royal Air Force and Royal Navy's results might well be of use to the graduating doctor going overseas or joining the active forces.

War burns differ considerably from those seen in civilian life, for treatment other than first aid may not be started for hours or even days after the receipt of injury. More are found on the hands and face than elsewhere. The chief cause of burns today is due to gunflash, bomb-flash, incendiary explosions, and chemicals.

In England Dupuytren's Classification has given way to the more serviceable and more easily handled classification suggested by Rainsford Mowlem. These bear some relation to treatment.

(1) Redness with or without some blistering

(2) Extensive blistering and partial destruction of the skin

(3) Complete destruction of the skin.

The degree of a burn cannot be told for certain until the fourth day after injury. All that can be noted before this is the presence of dermal circulation indicating first or second degree. Yellow-white colouration suggests the probability of a third degree burn.

Pathology

Little definite has been established yet. Serous exudation and a mild leucocytic infiltration is always shown in the first degree burn. The pathological picture in the case of death seems to depend on how early death occurs. The main feature, found in fourteen cases, death occurring 24-48 hours after injury, was marked Liver Necrosis. There was slight hepatomegaly and the liver was pale yellow, soft, greasy, and friable. There was marked degeneration in the central zone with often only a narrow strip of normal tissue remaining around the portal tracts. There may be fat-free sinusoidal haemorrhages and accumulations of eosinophils sometimes visible to the naked eye as yellow spots. The nucleii may show karyolysis. Nuclear inclusions, probably not of the virus type (Klötz), and Councilman Bodies are seen. These changes are indistinguishable from those found in the liver pathology of Yellow Fever and Rift Valley Fever. Congestion of brain, lung, spleen or adrenals was also found, but not characteristically.

Treatment of Shock in Burns

Primary shock seldom appears in burns and will be dismissed in passing. Secondary shock (6-8 hours) and its toxic phase (24 hours onwards) are, however, most important features, 80 p.c. of deaths occurring in this stage. The signs and symptoms are well known but the changes found are of interest as it is these that must be treated. The blood shows changes due to Plasma loss. The haemoglobin concentration rises; the serum protein falls; the chlorides fall, as does the sodium. The potassium will rise (17-23-30 mgm. p.c.). The CO_2 combining power decreases and there is a rise in urea and N.P.N. Changes also occur in the urine. Albumin, acetone, bile and casts may be found.

Therapy

Before starting any treatment morphine or amnopom (pantopon) must be given. Frequently the dose is 1/3 of a gr. and this may be repeated. A ¼ gr. may be given intravenously if necessary. Keep the patient warm with heat cradles and give oxygen with a B.L.B. mask raising the O_2 tension to 80 p.c. and thus reducing the incidence of fat embolism (44 p.c. found in fatal cases). The Plasma loss must then be treated. Intravenous serum or Plasma should be given, 2 to 4 pints usually being required. The first of

these should be given rapidly and the remainder at about 60 drops per minute. In cases of a dangerously low B.P. it was found by Pridie in Bristol (Eng.) that undoubtedly many lives were saved by injecting the first pint in three minutes under forced pressure from a Higginson syringe.

To deal with the protein and salt loss, the patient must be put on a high carbohydrate diet and salt given by mouth. Due to cortin deficiency, synthetic extracts of adrenal cortex have been found very useful in restoring blood sodium. There are many of these desoxycorticosterone acetate derivatives on the market. Some brands need to be given by intramuscularly injection, being oily; others are in watery bases and may conveniently be given with the intravenous drip. These DOCA products and the Pressor principle of pituitary extract are also of use in restoring the lowered B.P. Vitamin C is of use if any deficiency is present, as it tends to aid in detoxification, to protect the liver, and to decrease capillary permeability. 300-600 units should be given daily. The high carbohydrate diet also aids in protecting the liver. Vitamin P (hesperidin) has been given, but no beneficial results have been noted. A.T.S. (antitetanic serum) is *always* given.

Frequent check should be kept on haemoglobins, blood pressure, and urine, especially for urea if protein is being given in the diet. Death is likely to occur if the haemoglobin is above 115-120 p.c.

A useful method of calculating the amount of Plasma required to be given rapidly is to allow 250 ccs. for every 5 p.c. rise in haemoglobin.

Theories: the Toxic Effects of Burns

Many theories have been advanced but none seems to be quite adequate in itself.

(1) Aldrich suggested that the effect was entirely due to bacterial infection, especially the streptococcus haemolyticus.

(2) Underhill attributes the disturbances to the increased blood corpuscular concentration, as a result of the Plasma loss in the burned area. The viscosity is increased, circulation is impaired and stasis results.

(3) Wilson agrees with neither of these. He maintains that the toxic phase cannot possibly be explained by either or both. The liver damage is more severe than that caused by pure anoxia and bacterial infection. McClure and Russel Elkinton confirm this view and suggest that this is evidence of circulating non-bacterial toxin in the blood.

Burn Therapy

In the following treatments it will be seen that I have not mentioned sulphathiazole. This also applies to petrol (gasoline). This is due to the difficulty in obtaining these articles in England at the moment.

Three interesting facts may be stated here which will indicate the seriousness of burns: (i) The temperature in the cockpit of a Hurricane fighter in flames reaches 1200 degrees Fahrenheit in 8 seconds; (ii) Burns treated in the Royal Navy seem to be infected with either strep. haem. (Wakeley) or Staph. pyogenes aureus (Heggie); (iii) In U.S.A. before the war there were 8,000 deaths from burns per year—75 p.c. of these were due to carelessness. Many treatments have been suggested for burn therapy. Only some of these will be suggested and briefly commented on here.

All burns should be treated under anaesthetic. Gas and oxygen is adequate if no chest complications are feared. Pentothal and similar compounds may also be used.

Extensive First and Second Degree Burns

The skin here has not been completely destroyed. Therefore in the treatment three cardinal factors must be considered:

(1) Avoid further tissue damage
(2) Avoid and control infection
(3) Encourage epithelialisation.

First, this applies to all burns, local treatment in the form of antisepsis and debridement. The main function of this

is to separate non-viable tissue and prevent sepsis. Suffice it to say that soap and water, saline, ether and then saline may be used on the surrounding tissues. The burned area should be cleansed by foments, saline irrigation, saline packs or preferably baths, hydrogen peroxide and if necessary surgery. Trypsin seems to be useful but little work has been done in this respect. The burned area should be thoroughly dried in *all* cases with a hot air drier before any treatment is started.

Tan Treatment: with Tannics

Little can now be said for the plain tan treatment. It must not be used on the face, hands, near orifices or on flexor surfaces. The fear of tissue oedema and coagulum contraction causing obstruction to the blood supply, fibrosis or fixation of a joint seem to me sufficient to condemn its use. Besides this the tan may precipitate viable cells, cannot be readily removed if sepsis occurs beneath it and epithelialisation occurs slowly, forming only a poor and very vascular scar. Tannafax (tannic acid in a gum Tragacanth base) may be used therefore in small household burns. This too is the only place for picric acid 1 p.c.

If tannic acid preparations are to be used they should be used in the gel or spray forms, 2-10 p.c., and contain antiseptics such as Merthiolate or Brilliant Green (1:1,000). Hexyl-chloro-resorcinol (McClure) or Proflavine Sulphate (Heggie) are used, being strongly bactericidal and non-toxic to the cells. 5 p.c. $AgNO_3$ tends to speed up the tanning process if followed by 10 p.c. tannic acid (Wilson).

If blisters occur, they should at once be removed and painted with Brilliant Green. The edges of the coagulum should be painted with 1 p.c. Gentian Violet.

If sepsis occurs under the tan, it should be forcibly removed and other treatment started afresh. Hobson says healing will occur even if sepsis is present. If this is so treatment will be too prolonged.

Triple Dye Treatment

This is most suited to burns of the trunk owing to the semi-elastic type of coagulum obtained. It is unsuitable for third degree burns and does not stimulate rapid epithelialisation. The coagulum may be softened with glycerol but this seldom proves effective. 0.1 p.c. Acriflavine, 1 p.c. Brilliant Green, 2 p.c. Gentian Violet is sprayed on the clean and dry surface. This layer is dried and further applications applied. A fairly firm clot is obtained. This treatment could be used on the hands but other better and safer treatments are available.

The Bunyan-Stannard Treatment
(Lieut. Comm. Bunyan, R.N.)

This treatment is best suited to the limbs. It consists essentially of a watertight oilsilk bag fitting closely to the limb at its ends and having an entry and an exit hole. The clean limb is inserted into the bag, which is then filled with Milton (1 p.c. sodium hypochloride solution made by electrolytic process). If this becomes painful when the bag is only half full, the remainder may be filled with 0.85 p.c. saline. The bag is filled three times a day, the solution being allowed to remain in for fifteen minutes at a time. This removes all dirt and leaves the burn clean and is usually painless. The bag should always be flushed out and may be filled with oxygen when empty, but this seems unnecessary.

The advantages of this method are numerous. It is clean, cheap and removes all septic matter. Pain disappears rapidly and fluid loss is controlled. There is no unwieldy coagulum and thus no possibility of circulatory obstruction. Nursing is relatively easy and progress can be watched through the transparent bag. Electrolytically made hypochloride is proteolytic and appears to stimulate epithelialisation. As there are no dressings, there is little chance of cross infection.

Oil Treatment

According to results obtained so far carron oil or cod liver oil emulsion treatments appear to be very effective. Much research has been done lately on this

subject by Clayton, Howard, and Thomson. The treatment depends on the physico-chemical reaction. McIndoe has shown that the tan produced over a burnt area is too impervious and tough. Pus tends to accumulate beneath it. The idea in the tan treatment was to seal off the burnt area from outside infection, to reduce pain and to prevent fluid loss. At the point of contact between tissue and tan an interfacial film is formed. This interfacial tannic acid/protein membrane is hydrophilic. An interfacial oil/protein membrane can also be formed. This is both hydrophilic and hydrophobic and is a film coagulum (see Lancet, March, 1941). This seems to be important.

Animal cells allow the passage of both water soluble and fat soluble substances to pass through to nourish the cell. The importance of this fact can be seen as regards this treatment. Good membranes of double permeability can be prepared.

The protein/tan coagulum involves stechiometric and absorptive relations. Thus the product may not possess the capacity to absorb toxic materials from the burn. The protein/oil film is a purely physico-chemical one and will therefore drain and absorb better. As yet, even the most effective concentration of a tan has not been settled.

Oils form interfacial protein/oil membranes. These will not influence primary shock but will quickly control secondary shock, cleanse the wound and stimulate epithelialisation. A closed plaster cast method of immobilisation treatment is often useful. The cast should be put on early with a Sulphonamide powder. A layer 1/32 of an inch thick will not cause any harm, but more may act as a foreign body.

The oil permeates the tissues, liquefies necrotic material and stimulates growth. The best type of dressing is that used by Löhr and Steel. It consists of lint soaked in an oil preparation and applied to cover the part amply. This is left on at least forty-eight hours, but the dry lint dressing covering it is changed at least once a day. The bactericidal action of the oil is raised by Ultra-Violet light. Unsaturated components in the oils will be of the greatest value. To prevent rancidity, anti-oxygens (best of the phenolic type) must be incorporated.

Emulsions seem to give better results than pure oil. These must be of a water-in-oil type, the oil being in the continuous phase (an oil-in-water emulsion would be ineffective as dilution of the emulsion would occur on contact with the body serum) carron oil is a suitable emulsion, containing linseed oil and lime water (1:1). The calcium ions in this preparation influence greatly the permeability of the interfacial membrane.

Carron oil may be used as such. If cod liver oil is used it must contain lime water (1:1), an emulsifying agent such as Protegin (5 p.c.) and a dispersing factor such as Lanolin. A local anaesthetic may also be incorporated. Many proprietary brands containing various vegetable oils can be obtained both on this continent and in Europe.

This treatment is best suited to the limbs or trunk but if carefully applied may be used on both hands and face.

Saline Treatment

This is very suitable for both hands and face. The bath form should be used where possible, but where position prohibits, saline packs should be used. The baths should be given for at least 4 hours each day, the temperature being kept at 105 degrees Fahrenheit. Movement should be encouraged from the first. On moving from the bath a tulle-gras dressing should be applied. Saline packs should be put on over this. The tulle-gras should never be taken off but allowed to float off in the bath. If pack treatment is being employed they should be applied either direct or over tulle-gras. Sulphonamide powder should be used under the dressing at least once a day.

Tulle-gras dressing originated in France. It consists of close-meshed curtain net cut into suitable and varied sizes. This is immersed in a soft paraffin base and contains 1 p.c. Balsam of Peru and 1 p.c. fish or vegetable oil. Local anaesthetic is usually added in the form of Decicain or Percaine. The newer tulle-gras has Sulphonamide or Sulphonamide E-O-S (ethylorthosulphonate) already

added, but Sulphonamide dusting is just as effective.

Sulphanilamide-Gelatin Treatment

This treatment has not yet appeared in print, but is being tried out, seemingly effectively, by Mowlem at Hill End Hospital, St. Albans, England (this is the base hospital of St. Bartholomew's for civilians and military. Most of the patients are R.A.F. pilots).

A mixture of gelatin and 15 p.c. Sulphanilamide is sprayed onto the uncleaned, untreated, burnt area. This is done even in the worst and dirtiest situations. A gauntlet is formed as in the case of tannic acid, but here it is pliable. The greatest advantage, if need should arise, is that it can be removed in a few moments by moistening with saline.

This treatment obviates the necessity of doing a surgical debridement completely. The body proteins are not coagulated as is the case with tannic acid. Results so far obtained are highly satisfactory.

Penicillin, 1929

This is a product of the mould Penicillium and is highly active against Gram positive bacteria. It has been used in the treatment of burns but not sufficient results are yet obtainable. It is interesting to note, however, that as a bacteriostatic substance, it is 4 times as potent as Sulphathiazol and 100 times that of Sulphanilamide.

Special Burns

Burns of the Eyes

Large doses of morphine are always needed. The burns should be treated as ulcers. Sepsis is nearly always present and should be treated before anything else. This should be treated with an acetyl Sulphonamide ointment in a glycerol type of base. Later when clean treat with cod liver oil drops or 1 p.c. Scarlet Red in cod liver oil. Staphyloma should always be watched for.

Tannic acid treatment should never be used on or near the eyes. It will cause contraction of the lid, causing the margin of the eyelid to roll outwards (Ectropion) and this is usually followed by corneal ulceration. If perforation occurs panophthalmitis will probably result.

Burns of the Hands

Probably the best treatment is either the Sulphanilamide-Gelatin, Saline bath, or Bunyan-Stannard type. Of these probably the saline treatment is at the moment most serviceable although it entails careful nursing. It is carried out in the method already described with a bath every 2 to 3 hours. The dressing may consist of Acriflavine or Euflavine if preferred. Local sepsis is treated by Sulphonamide powder applied by insufflator.

Tannic acid treatment should never be used on the hands or fingers. Gross deformities and loss of the terminal phalanges readily occur if circulation is interfered with. Interesting photographs to this effect may be seen in last year's (1941) Proceedings of the Royal Society of Medicine.

Septic Burns

Nowadays burns should never be allowed to become septic. Even in the navy where treatment may be long delayed, first aid treatment with Gentian Violet and Merthiolate jelly is usually fairly effective. Give Sulphanilamide about vi grams daily by mouth, as well as local application of the powder. Better still is the local application of Sulphathiazol: Sulphanilamide (1:3). This gives quite a high local concentration. Do not use local Sulphapyridine as absorption is slow. Pure Sulphathiazol powder is excreted too quickly as well as being hard to get. The blood concentration of Sulphanilamide should be kept around 12 mgm. p.c.

Incendiary Burns

A phosphorus burn is often the main cause of injury. Therefore the burn should be irrigated first with 2 p.c. copper sulphate solution. This will neutralize the phosphorus effects. Ordinary burn therapy is then instituted.

Skin Grafting

I do not propose to go into the subject of skin grafting. Each surgeon favours his own type. It should, how-

ever, be started as early as possible, for the longer the clean surface is left the greater will be the fibrosis and contraction around the burnt area. Small, deep, third degree burns should be allowed to heal without skin grafting. Electrical burns will practically always need skin grafting.

After-Treatment

Lanolin should be rubbed into the new skin for at least six weeks after firm healing has taken place. This tends to prevent keloid scarring and keeps the skin supple and promotes a better blood supply. Keloid scars are particularly prone to occur with third degree burns or bad treatment.

Summary

To my mind the most important feature in the treatment of burns is the treatment of secondary shock. This should be carried out to the full, carefully and methodically in every case of severe burning. In the treatment of the burn itself the whole problem lies in the cleaning of the burned area and freeing it from toxic material which should never remain under a dressing. Tannic acid seems to be contra-indicated in nearly every case, except when in very experienced hands. The open type of treatment or an easily removable coagulum are the best treatments we have at the moment.

I should like to express my gratitude for the help given to me by Mr. Rainsford Mowlem of St. Bartholomew's Hospital and Flt/Lieut. P. G. Todd on the subject of treatment, to Dr. Duffin on the subject of the pathology, and to Dr. Danis in the presentation of the article.

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Feature Section

J. B. ROBERTS, Editor

ORTHOPAEDIC SURGERY

By R. I. HARRIS

Chief of Orthopaedic and Fracture Service, T.G.H.

The day has passed when all of surgery can be mastered by any one surgeon. The increasing complexity of modern surgery and the constant widening of its boundaries make it impossible for one individual to keep abreast of everything. Hence surgeons, even though they call themselves "general surgeons", limit their activities to the field in which interest or circumstance has given them greater mastery. The surgeon who desires to be a master is compelled to limit his interest and activities. He cannot otherwise achieve that mastery of his work which will enable him to advance knowledge beyond its present confines. By such evolution, the more technical and highly specialized fields have separated themselves from general surgery in order that skilled practitioners might become still more skilful; in order that knowledge in a particular field might be advanced and in order that teaching of that particular branch of surgery might be as perfect as possible.

While there is something to regret in this division of surgery into specialities, it is inevitable. In no other way is it possible to maintain the highest standards in every field of surgery or so readily to advance our knowledge. It has been occurring since the beginning of modern surgery. Gynaecology was the first of these special fields. Its differentiation came so early that it actually preceded general surgery as we know it to-day. Before Lister's antiseptic methods made modern surgery possible, bold pioneers like Spencer-Wells were demonstrating that the abdomen could be opened and the ovaries removed with little risk. In its early days, antiseptic surgery was largely gynaecology; only later were other regions of the body invaded by the surgeon. Then as surgery became more complex, ophthalmology, otolaryngology, neurosurgery, orthopaedic surgery, plastic surgery in turn have become specialties and have justified their existence by the advances they have achieved. The youngest member of the specialties is thoracic surgery.

It is interesting to watch the growth of a branch of surgery into a specialty. Not so many years ago the late Harvey Cushing was awarded the Charles Mickle prize of the University of Toronto for his outstanding work in neurosurgery. He came here and gave the lecture which the deed of gift stipulates he must deliver, but he refused to accept the thousand dollars which was the prize. Instead he suggested to the Professor of Surgery (the late C. L. Starr) that he give this to some young man of his choice to finance a year of study in Boston where he undertook to teach him the specialty of neurosurgery. In due course, the young man came back from Boston with his year's training in neurosurgery. Shortly he secured an appointment on the staff of the General Hospital. I can remember the difficult decision which then had to be made. Should he be given charge of a neurosurgical service or should he be a general surgeon to whom such neurosurgery as might turn up was sent? The latter plan was adopted on the grounds that there was not sufficient neurosurgery to keep one man busy. The decision was not so unreasonable as it now sounds. In all the years in which surgery had been practised in Toronto up to that time, only five patients with tic douloureux had been operated upon. Yet within a year of his return, the young neurosurgeon had operated upon thirty-five such cases and within a few years was performing one hundred and fifty major neurosurgical operations a year. One of the justifications of specialties is

that it broadens surgery, each specialty in its own field, so that the pathology of disease is clarified, new treatment is devised and for the first time new aspects of disease are brought under surgical control.

Like the other specialties, orthopaedic surgery has separated itself from general surgery in order that its practitioners might devote themselves more completely to the technical complexities of the surgery of the bones and joints, and of deformities. The growth of interest in this field of surgery is due chiefly to one man, the eccentric Hugh Owen Thomas, and the establishment of orthopaedic surgery as a specialty is due in large part to his son-in-law Sir Robert Jones. Thomas elucidated many of the problems of bone and joint disease, and devised new and fundamentally important principles of treatment. Sir Robert Jones applied these principles of treatment with such success that when the Great War came, it was he to whom authorities turned for guidance in the management and treatment of the orthopaedic problems of war. Since a great proportion of war wounds involved the skeletal and locomotor system, the amount of orthopaedic surgery involved was very great. It was handled supremely well in orthopaedic hospitals established by Sir Robert Jones. The stimulus of the last war enormously accelerated the growth of the specialty of orthopaedic surgery.

In surgery there is an element of craftsmanship which is lacking in internal medicine. The physician is a philosophical thinker and skill of his hands is of little importance to the practise of his art. In surgery it is otherwise. That part of the art connected with treatment is concerned to a considerable degree with craftsmanship. Technical skill, it is true, is a poor substitute for judgment. Any doctor can operate, even skilfully, but only a true surgeon knows when not to operate. Also it is true that tissues which are sutured together heal whether the sutures be neatly placed or not. Nonetheless there is a place in surgery for the display of skilful handiwork and if not essential for good results, at least it is a factor in obtaining improved results. Often, of course, success or failure, even life or death, is dependent upon the skill displayed in operating. In no field of surgery (save perhaps plastic surgery) is this more true than in orthopaedic surgery. It is, above all things, craftsmanship surgery. Success which justifies the operation is dependent upon niceties of technique and refinement of results. It is moreover a field in which the immediate postoperative result is not the final result. Long experience and far sighted planning, as well as skilful surgery, are necessary to secure the improvement in structure and function which are the aim of treatment. By its nature it attracts surgeons who are interested in craftsmanship.

This Toronto school of surgery has been conspicuous in its opposition to the narrowing trend of specialism and rightly so. The great defect of specialism is that in the course of time it tends to develop exponents whose experience is narrow and limited to their specialty. Young men leave medical school and at once begin the study of a specialty. Carried to extremes this can result in developing specialists with very narrow experience. The very justification of specialism may then be defeated. If specialism is necessary and wise to advance our knowledge in particular fields it must at least be based on broad surgical training. Otherwise the inter-relationships of one field with another will be lost and progress in one field have no significance or application in another. The way to become a good orthopaedic surgeon is to be a good general surgeon first and then to follow the trend of one's interests into the special field of orthopaedic surgery. Such evolution of able men has been responsible for the conspicuous position our school of surgery has occupied in the field of orthopaedic surgery under the leadership of the late C. L. Starr and of Professor Gallie. If we cannot all be leaders of orthopaedic surgery while still practising as general surgeons, at least we can be sure that our practice of orthopaedic surgery is based on a broad foundation of knowledge from every field of surgery.

The field of orthopaedic surgery is expanding. Industrial surgery and traffic accidents have added great numbers of orthopaedic cases to our wards. Our

knowledge of disease in the field of orthopaedic surgery is increasing and new vistas are opening for the application of orthopaedic surgery to the cure of disease. The future of the specialty is assured even without the stimulus which may come to it as a result of the war. It is a great and stimulating field of work, replete with problems demanding a surgeon's best for their solution. There is much gratification to a orthopaedic surgeon in the outcome of his work. His patients walk when before they crawled; stable limbs on which they stand erect replace the limp and helpless legs. And in the work itself a craftsman can find the pleasure and satisfaction which comes from good work well done.

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Abstracts

D. P. BRYCE, Editor

Contributors { J. G. Mickler, R. J. Wilson, G. G. Caudwell

Lymphatic Leukemia

Wiseman, J.A.M.A., 118, No. 2

The author claims that the lymphocyte must be recognized as a separate distinct strain of cell and not be confused with those of the reticuloendothelial system.

When this is appreciated there are then only two basic noninfectious diseases of the lymphocyte. Both are always at some time associated with qualitative or quantitative change in the lymphocytes in the peripheral blood. However one is neoplastic in origin and the other is neither neoplastic nor infectious but may be metabolic in origin. Both types occur with and without lymphemia.

The first of these is lymphosarcoma which is basically a leukemic state. About half of these cases show severe anemia in the onset, often without associated adenopathy or splenomegaly. The bone marrow is replaced with neoplastic cells although the blood picture may first be that of pernicious anemia only, later to be followed by a lymphemia of neoplastic lymphocytes. There may be excessive thrombocytopenia with hæmorrhages, which may lead to a diagnosis of thrombocytopaenic purpura or even of acute abdominal conditions if the haemorrhages occur in the intestine.

To diagnose this condition before lymphemia appears, therefore, one must frequently have recourse to the bone marrow. When lymphadenopathy is present biopsy may be of value.

The second large main division is that of lymphatic leukemia proper, in which when lymphemia is present and there is a specific alteration in the differential count no diagnostic problem exists. When there is no lymphemia the blood shows only minor changes although a qualitative change in the circulating lymphocytes may be detected. Changes in the lymphatic tissues are similar to those that occur with lymphatic leukemia and lymphemia. This condition is frequently confused with Hodgkin's disease clinically and lymphosarcoma pathologically. Clinically there is generalized lymphadenopathy with apparent good health. The bone marrow reveals a variable lymphoid count which when it is over 25% is diagnostic. An urticarial or patchy erythematous rash is common at some time during the disease. This disease can be kept under control for long periods by radiological treatment.

Thus before diagnosis the clinical facts, the blood picture, the condition and picture of the bone marrow, and the microscopic condition of the lymphatic tissue must be known.

D. P. B.

Lymphogenous Leukemia

Bethell, J.A.M.A., 118, No. 2

Lymphogenous leukemia comprises a group of pathologic states which have as their common attribute disordered and continued proliferation of lymphocyte forming tissue not limited in response to any recognized irritant or other stimulus, and manifested by continuous or intermittent alteration in the lymphocytes of the circulating blood.

It is further possible to classify these patients into three main groups on the basis of the type of lymph cell concerned, i.e., the lymphoblast, the lymphocyte, and the lymphosarcoma cell.

Lymphoblastic leukemia is a disease of childhood affecting twice as many males as females and characterized by anemia, fever, a tendency to uncontrollable hemorrhage and susceptibility to infec-

tion. Enlargement of the peripheral nodes is not an early feature of this type and treatment is mainly palliative with frequent transfusions. Duration is usually less than four months.

Lymphosarcoma cell leukemia predominantly affects males at any age. Enlargement of the peripheral nodes and spleen is an early feature. Roentgen therapy is often of value although severe toxic symptoms and reactions tend to be prevalent.

Lymphocytic leukemia affects more males than females and occurs almost exclusively in the middle and later years of life. Its course may be relatively benign. Anemia, debility and pressure symptoms are indications for roentgen treatment which may be given in 8 or 12 daily doses to the peripheral lymph nodes, the mediastinum, the retroperitoneal region, and the spleen.

Instead of roentgen therapy, liver extracts, Lugol's solution or Fowler's solution have been used.

D. P. B.

Chronic Constrictive Peucarditis Medical and Surgical Aspects

B. S. Oppenheimer, William M. Hityig, Harold Neuhof

Journal of Mt. Sinai Hospital, 7, 270-293

This disease is an extrinsic form of heart disease in which scars representing a thickened, contracted, and at times calcified pericardium, incarcerate and compress the heart, interfering with its diastolic expansion, less markedly with its systolic contraction. It may be idiopathic, tuberculous, follow pneumonia or rarely rheumatic fever. The symptoms are due to the constriction of the heart.

The diagnosis is greatly helped by Beck's triad, viz.:

(1) Small quiet heart
(2) Venous hypertension
(3) Ascites and a large liver

with other findings of passive congestion.

Once diagnosed the patient should be operated on, and the final results have been good in most cases.

D. P. B.

The Miller-Abbott Tube in Surgery

Leigh and Diefendorf

J.A.M.A., 118, No. 3

Miller-Abbott intubation has reduced the mortality and morbidity of ileus to a new low. It is to be considered as an adjunct to proper surgical care. In cases of strangulated hernia or gangrene immediate operation must still be advised.

Small bowel obstruction may be inflammatory or non-inflammatory, and each of these may be mechanical or paralytic in type. The intubation allows the water balance to be restored and by reducing tension improves the condition of the bowel and makes it fit for operation. Further by reducing the collected secretion in the distended bowel it allows of the use of barium and makes diagnostic X-ray effective. In infective lesions reduction in distension improves circulation and combats the infection so that edematous obstruction may be relieved and fibrous adhesions prevented.

Prophylactic intubation in cases where prolonged impairment of gastrointestinal mobility is involved, such as extensive colonic resection and peritonitis relieves tension and reduces the incidence of complications such as fistula formation. This early intubation has resulted in marked reduction of mortality from such conditions and has allowed of more single stage operations.

If gangrene is superceded by:

1. A history of sudden onset of pain that persists between attacks of crampy pain
2. Localized tenderness or palpable mass
3. An elevated pulse, temp., and white count which persists after fluids have been administered, then operation should be immediate. Even in these cases however a short period of intubation improves the prognosis greatly.

D. P. B.

Cesarean Section

Cosgrove and Norton, 118, No. 3

The indications for Cesarean section may be classified as A: Mechanical in-

terferences with labour—1, disproportion; 2, malpresentation; 3, dystocia due to soft parts; 4, tumours extrinsic to the uterus. B: Non-mechanical abnormalities peculiar to the pregnant state such as types of placenta previa, abruptio placentæ, and severe rapidly progressing toxemia. C: Disease conditions in the mother not primarily dependent on pregnancy, both medical and surgical in type.

Cesarean section must be decided upon in consultation. When conditions are elective the transperitoneal approach is best, on the basis of greater rapidity and facility of technique. Favourable conditions include complete lack of contamination, freedom from clinical evidence of infection, duration of total labour not in excess of twenty-four hours and duration of labour with ruptured membranes not in excess of 8 to 12 hours. When these conditions exist it makes no difference whether the high or low transperitoneal section are done.

When previous hopes of successful vaginal delivery are disappointed in labour, as they must sometimes be, then the only recourse is to one of the extraperitoneal Cesarean sections or to the Porro operation.

Over the last eight years they show a 2.5% incidence for section. They show a 44% morbidity for the classical section, a 49% for the low section, and a 70% for the extraperitoneal operation. In 68 cases of classical section their maternal mortality was 10% for all causes, although only 1 died of peritonitis.

Maternal mortality for the low section was .5% and for the extraperitoneal 2%. Fetal mortality for the same operations was respectively 20%, 8% and 5%. These figures however represent only the gross results and require further study to be significant.

D. P. B.

Dry After-Treatment of Infected Hands

Hamilton Bailey, *Lancet,* Aug. 16, 1941

This treatment has proven more satisfactory than hot baths and fomentations in the treatment of serious infections. It is used in conjunction with surgical drainage and chemotherapy. The infected finger is incased in a Visco paste bandage following surgical drainage and the insertion of a wisp of vaseline gauze. A Cramer wire is bandaged to the forearm and the whole suspended from an irrigator stand with the hand elevated. Flexion may be overcome by gradually extending the fingers closer to the splint each day. If the temperature is falling the dressing should not be disturbed for at least 48 hours.

After the fourth day, the vaseline gauze is removed, the hand washed in antiseptic solution and the wound irrigated, and the whole dried and the splint reapplied. After this period the arm is kept elevated for some days, being taken down only for rebandaging, daily finger exercises, and infra-red treatment.

If satisfactory progress is not being made, a rotation dressing may be applied every four hours in turn as follows — eusol, normal strength; hydrogen peroxide, 10%; magnesium sulphate, 5%; normal saline. After 48 hours, dry treatment is recommenced.

R. J. W.

Observations on Some Normal and Injurious Effects of Cold upon the Skin and Underlying Tissues

1. Reaction to Cold and Injury of Normal Skin.

By Sir Thomas Lewis

British Med. Journal, Dec. 6, 1941

If a person with skin temperature everywhere on the body within a few degrees of blood heat enters a cold room, the temperature of the skin begins to fall. In the absence of radiant heat, this will occur at from 16° to 20° C in most people. The cooling progresses until the skin temperature approaches that of the surrounding air. The parts of the body that cool most rapidly are the fingers and toes, then the ears and nose. The cooling takes one-half hour or more under normal circumstances. It is influenced by clothing, movement, movement of air

and other circumstances of exposure. Immersion in water lowers skin temperature much more rapidly.

Exposure to cold causes vasoconstriction of the skin vessels, blood flow is reduced and heat loss decreased. The response is complex and involves three separate reactions. First the vessels locally constrict in response to the cold. Then there is a general central vasoconstrictor reflex through the central-nervous system, which is transient. The third response occurs when cold venous blood returning from the skin, lowers the blood temperature in the general circulation and produces a persistent generalized vasoconstriction. These vasoconstrictions effect all vessels on the arterial or venous side.

The closing of the limb vessels while safeguarding against excessive fall of body temperature, ensures a fall of limb temperature, thus setting up a vicious circle in which limb temperature steadily falls toward environmental temperature. A fall to 10° C or lower always benumbs the skin so that touch and pain sense is lost, the muscles of the limbs are weakened by cooling of motor nerves and the proprioceptive mechanism is interfered with. Not only does the limb become inefficient but cooling beyond a certain point injures the skin.

The skin has its own local defense against this danger. If a finger is immersed in ice and water, the surface temperature falls rapidly to near freezing point in the course of a few minutes and becomes painful. After 5-20 minutes the pain lessens and the finger no longer feels cold. It becomes the seat of local vasodilation which raises the temperature of the still immersed finger 5-8° C. This process does not persist; the temperature falls, and the whole process is repeated. As a result the mean temperature of the finger is appreciably raised. This process is most marked in the feet, hands and face, but only to a small degree over the rest of the body. It depends upon a local axon reflex and is lost in from 6-10 days after cutaneous nerves have been cut, only to return after nerve regeneration. This reaction is vigorous at or near freezing point but is also in evidence at 15-18° C. It is probably a result of skin injury.

Excessive cooling may injure the skin in two ways, either by direct action or by causing it to freeze. The vasodilation may be a response to the H substance released by excessive cooling. The production of pain suggests injury and this occurs very close to the point where the axon reflex begins to have its effect. At the point of cooling a wheal is formed in some people. Prolonged cooling actually leads to edema in the skin and subcutaneous tissues. The limb may be red and swollen 15% in excess of its normal volume. This may return to normal in the course of a few hours. It can occur in a hand protected by a rubber glove or grease, or in water at 10 or 15° C. It is suggested that if several limbs were exposed over a long period of time, as might occur in a wounded soldier, sufficient fluid might be lost from the circulation to account, in part at least, for their frequent circulatory collapse.

R. J. W.

Intestinal and Mesenteric Injury due to Nonpenetrating Abdominal Trauma

D. Henry Poer, and Edward Woliver
J.A.M.A., Jan. 3, 1942, p. 11

This paper sets forth the results of studies on the surgical problems arising out of injuries to the intestine and mesentery by force which does not penetrate the abdominal parietes. In reviewing the literature it was found that such injuries had a high mortality rate. Of 1313 cases reviewed up to 1935, operation on 887 yielded a gross mortality rate of 60.7%. In 426 cases, diagnosis was established at autopsy, raising the total mortality to 73.4%. In 163 cases since 1935 the mortality was 50.4% in cases operated upon and 61.3% in all cases.

Three chief mechanisms were responsible for these injuries. The commonest method by which perforation is produced is by a crushing injury which compresses the bowel against the spine or pelvic bones. Occasionally tearing injur-

ies may result from violent force applied at a tangent to the body. Bursting injuries usually result from the introduction of compressed air into the anal canal.

Of the predisposing causes, hernia is the most important. The most frequent site was the ileum. The cases included 4 with multiple perforations, 3 of whom died, and 6 with complete severance of the gut, 5 of whom died. The most convenient classification included three groups:

A. Diagnosis and treatment were delayed for more than 12 hours, either because the patient thought the injury was trivial or because the physician failed to realize the seriousness of the situation. Mortality here 70%.

B. Diagnosis and treatment prompt. Mortality 35%.

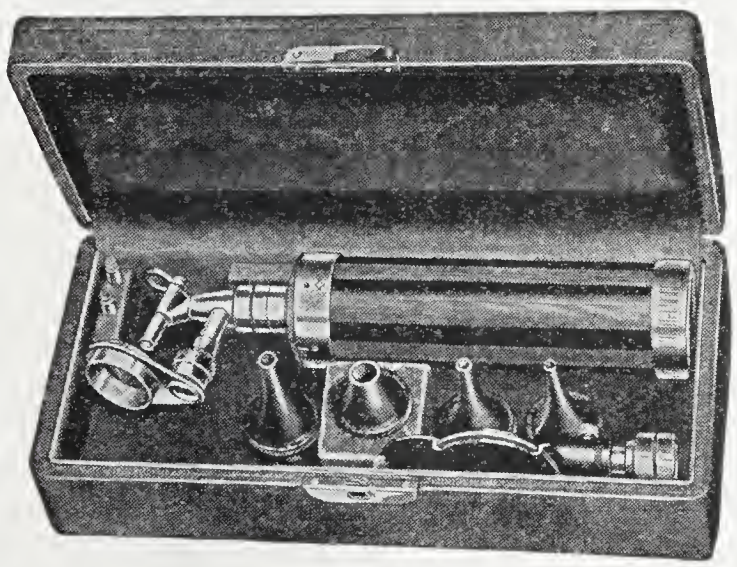
C. Multiple severe extra-abdominal lesions overshadowing the abdominal lesions. Mortality 100%.

The signs and symptoms are variable and frequently begin as peritonitis. Shock usually appeared with peritonitis, but in multiple severe cases was present at the onset.

The most constant symptom was abdominal pain and tenderness with rigidity. Next most reliable was a rising pulse rate. External evidence was present in only 16 of 36 cases.

Treatment must be early with preoperative correction of the fluid balance and treatment of shock. The operation should be prompt and as simple as possible. Post-operative care should include adequate intestinal decompression, regulation of fluid and electrolyte balance, and the use of sulphonamides.

R. J. W.



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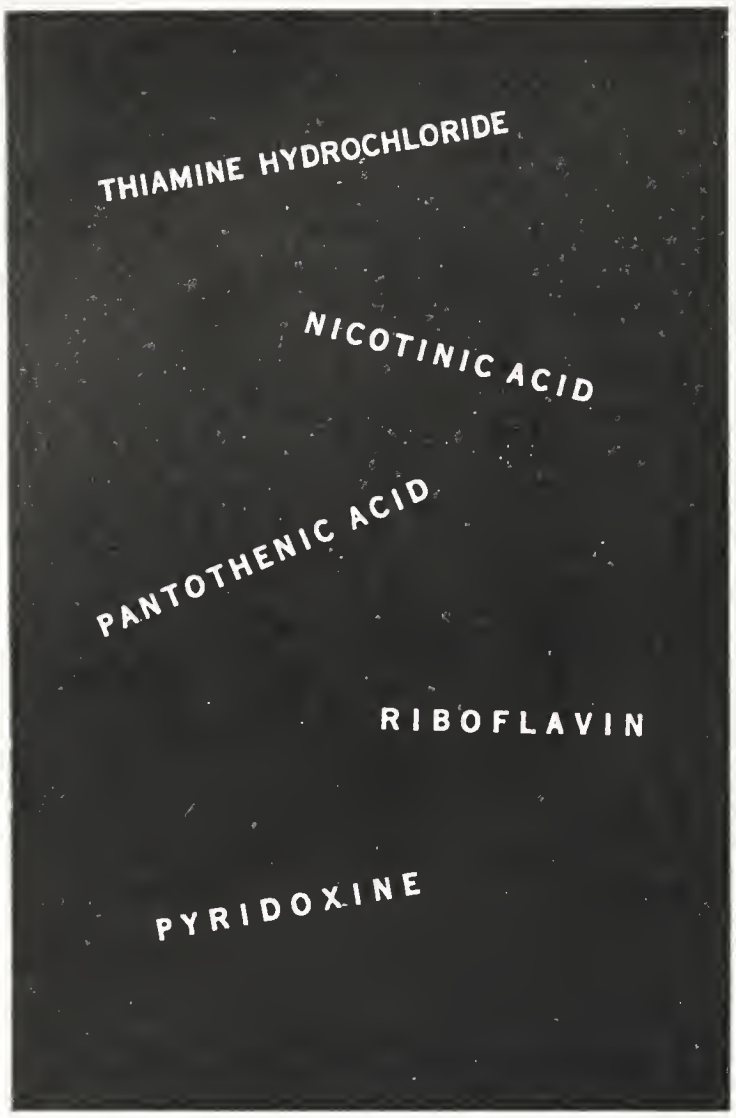

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